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# Long non-coding RNA MIR205HG regulates KRT17 and tumor processes in cervical cancer via interaction with SRSF1

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ABSTRACT

Abnormal expression of long non-coding RNAs (lncRNAs) has been demonstrated to be a vital regulatory factor in a large number of malignancies. The investigation in cervical cancer and the associated modulation mechanisms are yet to be probed. The aim of this study is to specifically investigate the expression pattern and modulatory mechanism of MIR205HG in cervical cancer. Our paper firstly revealed the up-regulation of KRT17 in cervical cancer. Function assays further displayed that KRT17 silencing impaired the proliferation and migration, and activated the apoptosis of cervical cancer cells. Based on the finding that MIR205HG could regulate KRT17 expression, we further probed the detailed mechanism between MIR205HG and KRT17. It was observed from mechanism experiments that MIR205HG depleted SRSF1 to increase KRT17 expression. The whole mechanism of MIR205HG/SRSF1/KRT17 axis affecting cell proliferation, apoptosis and migration in cervical cancer was validated using rescue assays. In conclusion, MIR205HG modulated the biological activities of cervical cancer cells via targeting SRSF1 and regulating KRT17, which better understood the pathogenesis of cervical carcinoma and excavated a novel therapeutic target.

## 1. Introduction

Cervical cancer is ranked as the fourth most common cancer and also the fourth most primary cause of cancer mortality in females all around the world (Bray et al., 2018). Nowadays, for Chinese women, an increasing trend of the occurrence and death rates for cervical cancer patients was observed (Chen et al., 2018; Chen et al., 2016; Schiffman and Brinton, 1995). Owing to the poor understanding of effective molecules-targeted therapy, the predominant treatments for cervical cancer are surgical resection, chemotherapy and radiotherapy (Regalado Porras et al., 2018). Hence, it is vitally meaningful for us to explore the molecular mechanisms under the initiation and progression of cervical cancer in case of the searching for persuasive diagnostic biomarkers or novel molecules in cancer progression.

The human genome is comprised of not only messenger RNAs (mRNAs) for protein translation, but also non-coding RNAs (ncRNAs) participating in the pathological processes of a variety of diseases (Eddy, 2001; Gao et al., 2019b; Xing et al., 2018). Long ncRNAs (lncRNAs), a group of ncRNAs, have been revealed to get involved in the pathogenesis of numerous tumors (Mercer et al., 2009; Ulitsky and Bartel, 2013). For instances, lncRNA EGFR-AS1 promotes cell growth and metastasis via affecting HuR mediated mRNA stability of EGFR in renal cancer (Wang et al., 2019); Long noncoding RNA HOXC13-AS positively affects cell proliferation and invasion in nasopharyngeal carcinoma via modulating miR-383-3pHMGA2 axis (Gao et al., 2019a); Long noncoding RNA MT1JP inhibits proliferation, invasion, and migration while promoting apoptosis of glioma cells through the activation of PTEN/Akt signaling pathway (Zhang et al., 2019c). Still and all, the specific participation of lncRNAs in cervical cancer is yet to be researched.

LncRNA MIR205 host gene (MIR205HG) is a newly recognized lncRNA that participates in the regulation of cellular processes of several cancers. MIR205HG depletes miR-590-3p causing unlimited proliferation of head and neck squamous cell carcinoma cells (Di Agostino et al., 2018). MIR205HG serves as a ceRNA (competing endogenous RNA) to promote tumor growth and progression through targeting miR-122-5p in cervical cancer (Li et al., 2019b). Even so, the seeking for more regulation mechanisms underlying MIR205HG in cervical cancer is needed.

The present study was performed to explore the involvement of

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MIR205HG in cervical carcinoma. Our paper firstly revealed the up-regulation of KRT17 in cervical cancer. Function assays proved that KRT17 silencing impaired the proliferation and migration, and activated the apoptosis of cervical cancer cells. As MIR205HG could regulate KRT17 expression, we further investigated the detailed mechanism between them. Mechanism experiments displayed that MIR205HG depleted SRSF1 to increase KRT17 expression. The whole mechanism of MIR205HG/SRSF1/KRT17 axis was affirmed by rescue assays.

## 2. Material and methods

### 2.1. Cell culture

CC (cervical cancer) cell lines (CaSki, MS751, HeLa and SiHa) as well as normal cervical cell line HcerEpic were purchased from American Type Culture Collection (Manassas, VA). And then cells were maintained in Dulbecco's modified Eagle's medium (DMEM; Thermo Fisher Scientific, Inc., Waltham, MA) containing 10% fetal bovine serum (FBS, Thermo Fisher Scientific), 100 U/ml penicillin and 100 mg/ml streptomycin. Cell culture was at 37 C with 95% air and 5% $CO_2$. Replacement of culture medium was conducted every third day.

### 2.2. Quantitative real-time PCR (qRT-PCR)

Using TRIzol reagent (Thermo Fisher Scientific, Inc.), total RNA was isolated from CaSki, HeLa, MS751 and SiHa cells as the supplier's instructions advised. Thereafter, the PrimeScript RT Reagent Kit (Invitrogen, Carlsbad, CA) or miRcute Plus miRNA First-Strand cDNA Kit (TIANGEN, Beijing, China) was used to reversely transcribe RNA into cDNA. The real-time PCR was performed using the SYBR Premix Ex Taq (TaKaRa, Dalian, China) on ABI 7500 real-time PCR system (Applied Biosystems, Foster City, CA). GAPDH was regarded as an internal control. U6 was used as an internal microRNA control. In addition, the comparative $2^{-\Delta\Delta Ct}$ method was applied for qRT-PCR.

### 2.3. Cell transfection

For performing cell transfection assay, PCR was performed to amplify the KRT17 full length sequence and then the pcDNA3.1 vector (Thermo Fisher Scientific, Inc.) was used to establish the pcDNA3.1-KRT17 overexpression plasmid (termed KRT17). The empty vector was seen as control. The expressions of KRT17, MIR205HG and SRSF1 were silenced by the specific short hairpin RNAs (sh-KRT17#1/#2/#3, shMIR205HG and shSRSF1) from Shanghai GenePharma Co., Ltd. (Shanghai, China). The non-specific shRNAs were taken as controls. CaSKi, Hela, MS751 and SiHa cells were plated in six-well plates for one day, transfected by use of Lipofectamine™ 2000 reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and collected after 48 h.

### 2.4. Cell counting Kit-8 (CCK-8)

The cell proliferation of CaSKi, Hela, MS751 and SiHa was detected using a CCK-8 assay kit (Dojindo, Molecular Technologies, Kumamoto, Japan). The cells were seeded into 96-well plates ($1\times10^3$ cells per well) in the dark at 37 °C with 5% $CO_2$ for 4 h, and 100 μL CCK-8 was added to each well at 0, 24, 48, 72 and 96 h. The absorbance was measured at 450 nm through a microplate reader (Bio-Tek Instruments, Winooski, VT), and the optical density values were recorded.

### 2.5. EdU assays

Firstly, CaSKi, Hela, MS751 or SiHa cells ($2\times10^3$) were seeded in 96-well plates, and then incubated overnight until they were fused up to 80–90%. Secondly, the 5′-ethynyl-2′-deoxyuridine (EdU) incorporation assay was performed to evaluate cell proliferation, and a KeyFluor488 Click-iT EDU kit (KeyGEN BioTECH, Nanjing, Jiangsu, China) was used. Lastly, the cells were visualized by using a fluorescence microscopy (Leica, Wetzlar, Germany), and the images of cells were captured and photographed.

### 2.6. Transwell assays

Transfected or control CaSKi, Hela, MS751 and SiHa cells in 24-well culture plate ($2\times10^4$ per well) were prepared in serum-free medium and then planted into the upper chamber, while the lower chamber was filled with DMEM containing 10% FBS. After 24 h of culturing at 37 °C with 5% $CO_2$, cells on the upper surface were removed with a cotton swab. The migrating cells were first settled with 4% paraformaldehyde and then stained with 0.1% crystal violet on the lower surface. Finally, the migrated cells were photographed and observed using an optical microscope. Five fields were randomly counted and the average was obtained.

### 2.7. Detection of Caspase-3 activity

A Caspase-3 activity kit (Beyotime Institute of Biotechnology, Shanghai, China) was applied in this study to examine the activity of caspase-3. CaSKi, Hela, MS751 and SiHa cells were cultivated in lysis buffer to obtain total protein. Protein samples were collected and put into 96-well plates and mixed with reaction buffer and caspase-3 substrate for 4 h. At length, the mixture was detected at the wavelength of 405 nm with a microplate reader.

### 2.8. RBP (RNA-binding protein) prediction

StarBase v3.0 (http://starbase.sysu.edu.cn/index.php) was utilized to select the RBP, SRSF1 (serine/arginine-rich splicing factor 1), which could bind with both MIR205HG and KRT17. Firstly, we searched and found out 12 RBPs that could bind with KRT17 by using StarBase, and then in a similar way, there were 12 RBPs possessing the binding possibility with MIR205HG. Finally, the intersection of the two groups of RBPs was screened out and it obviously seen that SRSF1 was the only RBP binding with KRT17 and MIR205HG.

### 2.9. RNA immunoprecipitation assay

RIP assay was conducted in this study using an Imprint RNA immunoprecipitation kit (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany). In brief, the lysates from CaSKi and Hela cells were incubated with anti-IgG or anti-SRSF1 overnight at 4 °C. After that, the magnetic beads were added to the aforesaid mixture to form a complex of immunoprecipitation. Next, the precipitated complexes were purified and then evaluated by qRT-PCR assay.

### 2.10. Statistical analysis

In our study, the numerical data were analyzed by SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) and expressed as the mean ± SD. *P*-values of at least three biological replicates were calculated by using *t*-test or one-way ANOVA, with the significant level of $< 0.05$.

## 3. Results

### 3.1. KRT17 was overexpressed in cervical cancer and KRT17 down-regulation obstructed the proliferation and migration, and induced the apoptosis in cervical cancer

The TCGA dataset predicted that KRT17 was elevated in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) tissues (Fig. 1A). Next, the high expression of KRT17 in cervical cancer cells (CaSki, MS751, HeLa and SiHa cells) was also detected by qRT-

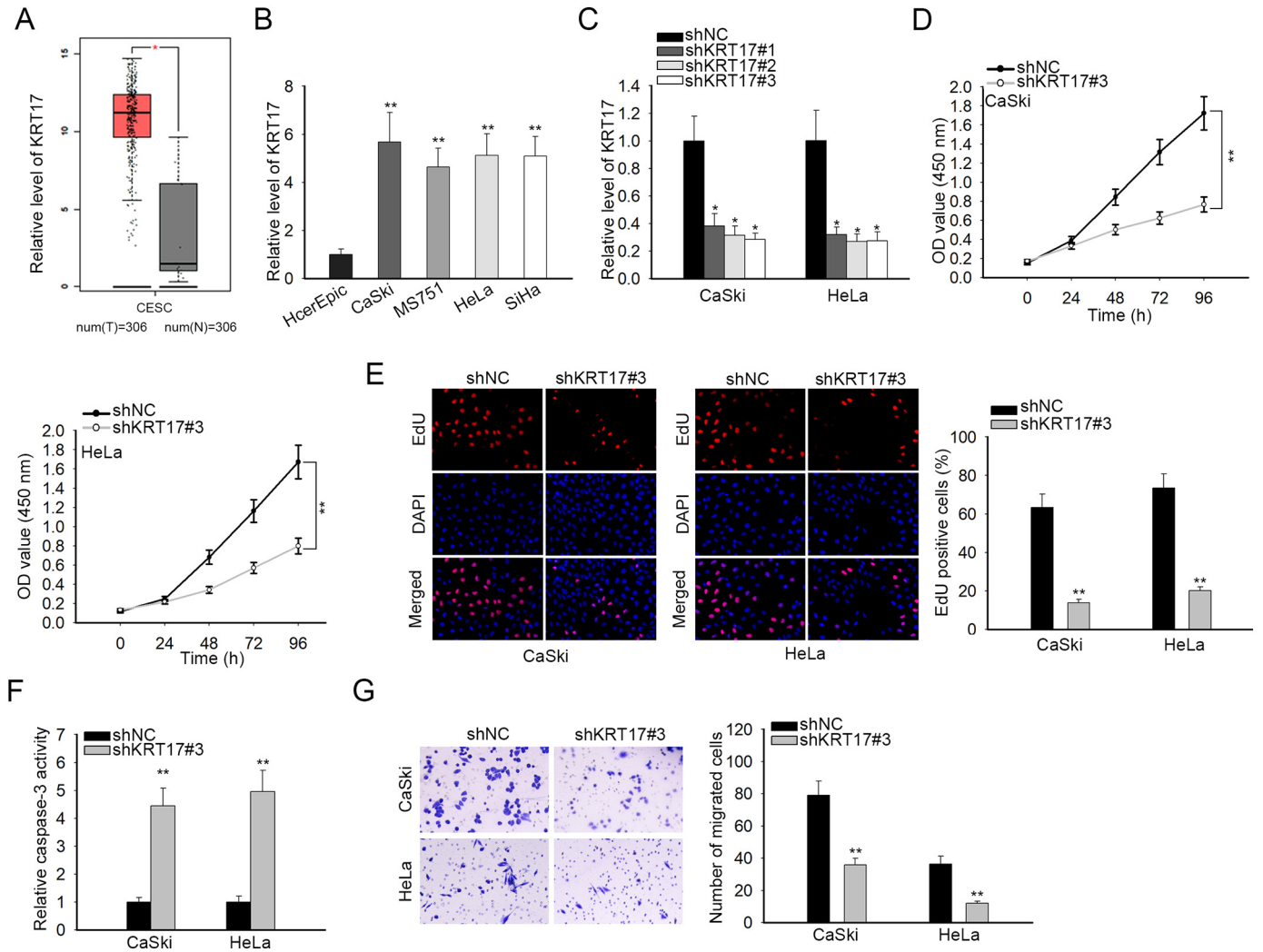


**Fig. 1.** KRT17 was overexpressed in cervical cancer and KRT17 down-regulation obstructed the proliferation and migration, and induced the apoptosis in cervical cancer. (A) KRT17 was overexpressed in CESC tissues, compared with normal tissues. (B) qRT-PCR analysis of KRT17 expression in cervical cancer cells (CaSki, MS751, HeLa and SiHa cells) and normal HcerEpic cells. (C) qRT-PCR results of the transfection efficiency of shKRT17#1/2/3. (D-E) Cell proliferation was determined by CCK-8 and EdU assays. (F) Caspase-3 activity assay was carried out for examining cell apoptosis. (G) Transwell assays were performed for examining cell migration. $^{*}P < .05$, $^{**}P < .01$.

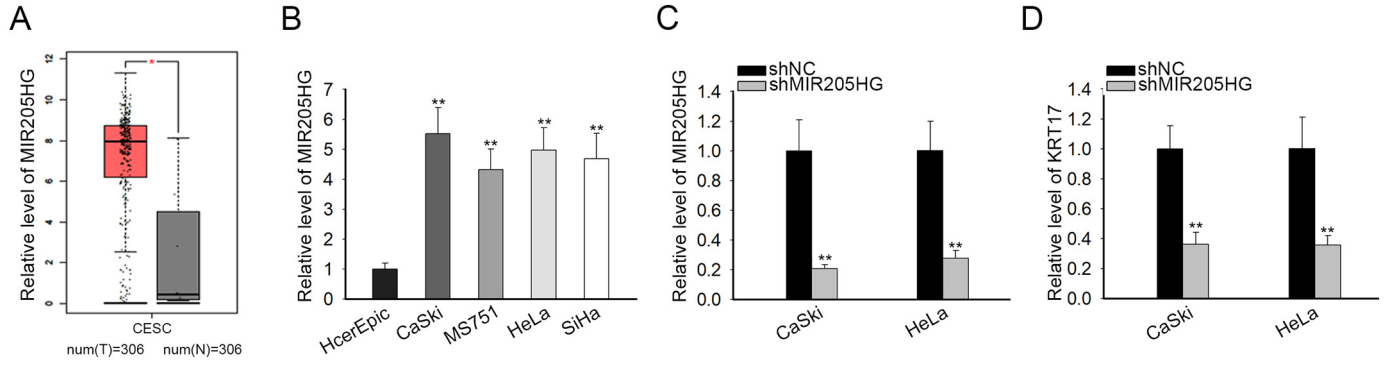


**Fig. 2.** LncRNA MIR205HG could regulate KRT17 expression. (A) MIR205HG was upregulated in CESC tissues, compared with normal tissues. (B) MIR205HG was also high in cervical cancer cells and normal HcerEpic cells, as estimated by qRT-PCR. (C) MIR205HG expression was significantly decreased by shMIR205HG. (D) KRT17 was knocked down by shMIR205HG. $^{*}P < .05$, $^{**}P < .01$.

PCR, in comparison with normal HcerEpic cells (Fig. 1B). Among tumor cells, HeLa and CaSki cells exhibited higher levels of KRT17. The shRNAs targeting KRT17 (shKRT17#1/2/3) were transfected into HeLa and CaSki cells for the silencing of KRT17 (Fig. 1C). CCK-8 results indicated that KRT17 silence inhibited cell viability (Fig. 1D). EdU assay showed that the proliferation was repressed when KRT17 was knocked down (Fig. 1E). As for the detection of cell apoptosis, the analysis of caspase-3 activity assay showed that cell apoptosis rate was

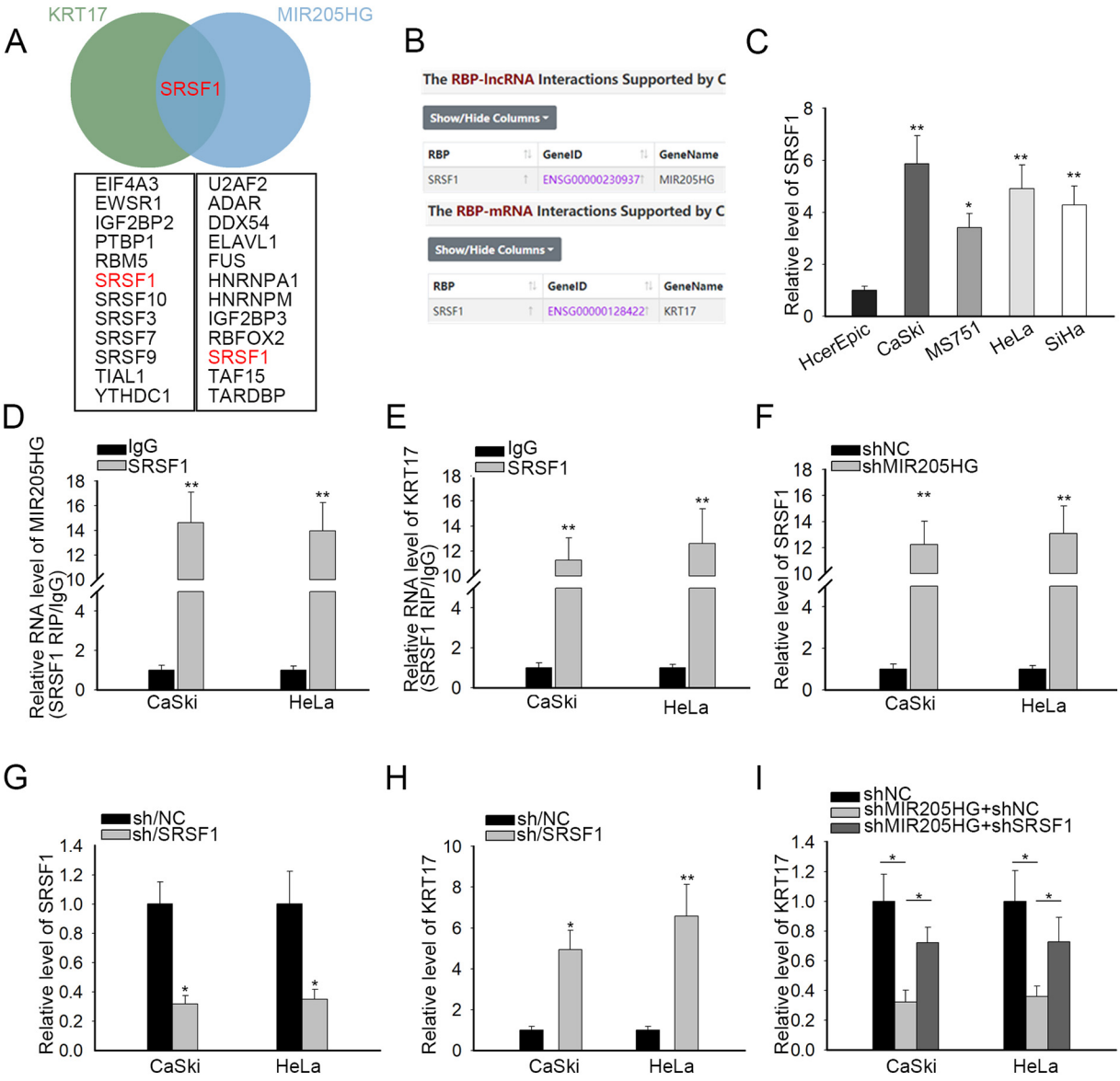


**Fig. 3.** MIR205HG bound to SRSF1 to regulate KRT17. (A) The Venn diagram of the 1 common RBP of MIR205HG and KRT17. (B) starBase v3.0 predicted that SRSF1 bound to both MIR205HG and KRT17. (C) qRT-PCR results of SRSF1 expression in cervical cancer cells and normal HcerEpic cells. (D-E) RIP experiments validated the interplaying between SRSF1 and MIR205HG or KRT17. (F) The impacts of MIR205HG on SRSF1 were determined through qRT-PCR. (G-H) The expressions of SRSF1 and KRT17 in shSRSF1 transfected cells were detected by qRT-PCR. (I) qRT-PCR was used to affirm the co-influences of MIR205HG and SRSF1 on KRT17. *P < .05, **P < .01.

increased through silence of KRT17 (Fig. 1F). In transwell experiments, the number of migrated cells was reduced by shKRT17#3, suggesting the inhibitory effect of KRT17 silencing on cell migration (Fig. 1G). Similarly, we also silenced KRT17 in MS751 and SiHa cells to detect cellular functions (Fig. S1A). Above mentioned functional experiments were re-performed in MS751 and SiHa cell lines (Fig. S1B-E), and the same conclusion were obtained. All in all, KRT17 knockdown hindered the proliferation and migration capacities of cervical cancer cells.

### 3.2. LncRNA MIR205HG could regulate KRT17 expression

LncRNAs are pivotal molecules that can mediate gene expression in various carcinomas (Guan et al., 2016; She et al., 2016). LncRNA MIR205HG was a predicted overexpressed lncRNA in CESC tissues by employed the public database GEPIA (http://gepia.cancer-pku.cn/index.html), as exhibited in Fig. 2A. Then the overexpression of MIR205HG in cervical cancer cells was confirmed (Fig. 2B). The exploration of MIR205HG in cervical cancer is inadequate till now and whether MIR205HG regulates cellular activities of cervical cancer cells through KRT17 is still an enigma. Hence, we experimented whether MIR205HG could affect KRT17 expression. After MIR205HG was silenced by transfection of shMIR205HG, KRT17 expression was also lowered (Fig. 2C-D). These data illustrated that MIR205HG modulated KRT17 mRNA expression.

### 3.3. MIR205HG bound to SRSF1 to regulate KRT17

RNA-binding proteins (RBPs) are one link associating lncRNAs with mRNAs (Jiang et al., 2017; Pereira et al., 2017). To find out the correlation between MIR205HG and KRT17, we browsed starBase v3.0 and selected SRSF1 (serine/arginine-rich splicing factor 1), one RBP binding with both MIR205HG and KRT17 (Fig. 3A-B). SRSF1 expression was also lifted in cervical cancer cells (Fig. 3C). Then the interplay between SRSF1 and MIR205HG or KRT17 was validated through RIP assays

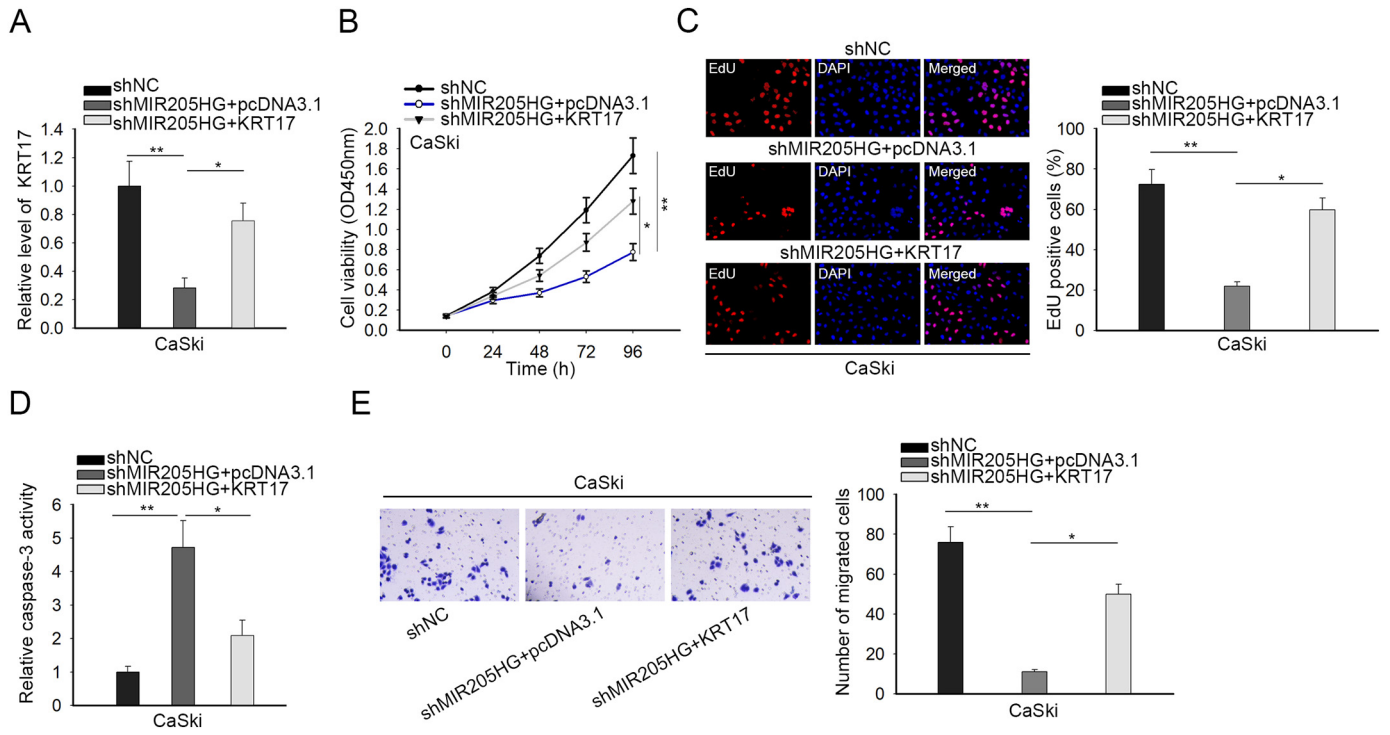


**Fig. 4.** KRT17 promotion reversed the repressive impacts of MIR205HG knockdown on biological processes. (A) The transfection efficiency in three groups was validated by qRT-PCR. (B−C) Cell proliferation of three groups was examined by CCK-8 and EdU assays. (D) Caspase-3 activity assay tested cell apoptosis in three groups. (E) Cell migratory ability was evaluated via transwell assay. *P < .05, **P < .01.

(Fig. 3D-E). Strikingly, SRSF1 expression was increased when MIR205HG was downregulated (Fig. 3F). And the knockdown efficiency of SRSF1 was tested in shSRSF1 transfected cells (Fig. 3G). Further, KRT17 expression was augmented when SRSF1 was knocked down (Fig. 3H). Here, we tested the co-effects of MIR205HG and SRSF1 on KRT17. The results discovered that MIR205HG down-regulation accordingly decreased KRT17 expression, which was recovered partly by SRSF1 inhibition (Fig. 3I). Taken together, MIR205HG relieved KRT17 from the splicing by SRSF1.

### *3.4. KRT17 promotion reversed the repressive impacts of MIR205HG knockdown on biological processes*

Rescue assays were carried out through respective infection of shNC, shMIR205HG + pcDNA3.1 and shMIR205HG + KRT17 (Fig. 4A and Fig. S2A). Based on the detections of CCK-8 and EdU assays, it was obvious that cell proliferation was hampered through MIR205HG inhibition but rescued through KRT17 promotion (Fig. 4B-C and Fig. S2B-C). Caspase-3 activity assay revealed that MIR205HG repression induced cell apoptosis and this effect was weakened under the co-transfection of KRT17 overexpression (Fig. 4D and Fig. S2D). Transwell assay demonstrated that the obstructed cell migration by shMIR205HG was regained in part by KRT17 upregulation (Fig. 4E and Fig. S2E). In addition, as shown in Fig. S2, the rescuing experiments were also carried out in HeLa cell to further prove above findings. Totally, MIR205HG regulated cell proliferation, apoptosis and migration in cervical cancer via KRT17.

## 4. Discussion

To seek for effective molecules in the processes of cervical cancer, we scanned the cancer genome atlas (TCGA) dataset and observed the most significantly high expression of Keratin 17 (KRT17) in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) tissues. Past studies have indicated that KRT17 is an oncogene in numerous human tumors, including Ewing sarcoma (Sankar et al., 2013), oral squamous cell carcinomas (Mikami et al., 2017), lung adenocarcinoma (Liu et al., 2018), gastric cancer and cervical cancer (Chivu-Economescu et al., 2017; Li et al., 2019a). Consistently, KRT17 was highly expressed in cervical cancer cells and the silence of KRT17 repressed the proliferative and migratory abilities and promoted the apoptotic ability in cervical cancer. Our research, for the first time, revealed the expression profile and carcinogenic function of KRT17 in cervical cancer.

Many long non-coding RNAs (lncRNAs) have been demonstrated to be aberrant and develop tumor-repressive or inhibitory function in the progress of carcinomas. For examples, GHET1 works as a prognostic indicator and a carcinogenic lncRNA in cervical cancer (Zhang et al., 2019a); lncRNA-OIS1 represses HPV-positive, but not HPV-negative cervical squamous cell cancer by up-regulation of MTK-1 (Zhou et al., 2019a); lncRNA-TCONS_00026907 participates in the prognosis and progression of cervical cancer cells via miR-143-5p inhibition (Jin et al., 2017). LncRNA MIR205 host gene (MIR205HG) has been reported to promote cell proliferation in head and neck squamous cell carcinoma and accelerate tumor growth and progression in cervical cancer (Di Agostino et al., 2018; Li et al., 2019b). In this research, MIR205HG was found to regulate KRT17 expression, which prompted us to inquire the unexplored mechanism between MIR205HG and KRT17.

RNA-binding proteins (RBPs) are known to regulate gene expression at post-transcription level (Glisovic et al., 2008; Kim et al., 2009). Mounting evidence has exposed the relationship among lncRNAs and mRNAs through RBP interactions (Barbagallo et al., 2019; Li et al., 2017; Zhang et al., 2019b). Only one RBP, serine and arginine rich splicing factor 1 (SRSF1), shared by MIR205HG and KRT17 was found from starBase v3.0, and then we chose SRSF1 for deep-going investigations. According to previous studies, SRSF1 could exert oncogenic roles in many carcinomas. For instances, oncogenic RNA-binding protein SRSF1 modulates LIG1 in non-small cell lung cancer (Martinez-Terroba et al., 2018); SRSF1 inhibits DNA damage and enhances tumorigenesis by regulating DBF4B pre-mRNA splicing (Chen et al.,

2017); SRSF1 boosts glioma tumorigenesis through oncogenic splice-switching of MYO1B (Zhou et al., 2019b). The current research proved that MIR205HG regulated KRT17 through binding to SRSF1. Finally, rescue experiments certified the regulatory mechanism of MIR205HG/SRSF1/KRT17 axis in cervical cancer.

In conclusion, MIR205HG modulated the biological activities of cervical cancer cells via targeting SRSF1 and regulating KRT17. Our investigation shed novel lights into the pathogenesis of cervical carcinoma and excavated a novel therapeutic target for cervical cancer therapy.

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## Declaration of Competing Interest

Authors declare there are no conflicts of interest in this paper.

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